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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,438	04/11/2006	Christopher Wheeler	22862-004US1 / 67789-570	4024

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EXAMINER	
GODDARD, LAURA B	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,438	WHEELER ET AL.	
	Examiner	Art Unit	
	LAURA B. GODDARD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-7,10 and 11* is/are pending in the application.

4a) Of the above claim(s) *4 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-7,10 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/21/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The Amendment filed February 19, 2008 in response to the Office Action of October 18, 2007, is acknowledged and has been entered. Previously pending claims 1 and 3 have been amended. Claims 8, 9, and 12-20 are canceled. Claims 4 and 21-24 remain withdrawn. Claims 1, 2, 3, 5, 6, 7, 10, and 11 are currently being examined as drawn to the elected species of chemotherapeutic "temozolomide," and the species of dendritic cell "primed".

New Rejections

(necessitated by amendments)

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1-3, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent Application Publication 2002/0119121, Vitiello et al, filed 9/6/2001, published 8/29/2002, in view of Friedman et al (Clinical Cancer Research, 2000, 6:2585-2597).

The claims are now drawn to a method for treating a disease condition in a mammal, the method comprising: administering at least one vaccination of dendritic cells (DC) to said mammal; and administering a regimen of chemotherapy to said mammal, wherein said administering of at least one vaccination of DC occurs prior to administering said regimen of chemotherapy to said mammal, and wherein said regimen of chemotherapy includes the administration of at least temozolomide (claim 1), wherein said DC are primed *ex vivo* (claim 2), wherein said DC are autologous and wherein said DC are tumor antigen-presented DC (claim 3), wherein said disease condition is a cancer of the central nervous system and is glioblastoma multiforme (claims 10 and 11).

It is noted the specification discloses that a "disease condition" includes cancer (p. 7, [23]).

Vitiello et al teach a method of treating cancer in a patient (mammalian) comprising administering DC to a patient prior to, during, or subsequent to chemotherapy treatment ([2]; [83]; [135]; [140]), wherein the DC are autologous and primed *ex vivo* with tumor antigens from the patient ([36]; [59]; [65-72]; [79-83]; [96]; [99]; [102-103]; [114]), wherein the cancer is glioblastoma multiforme ([51]; Table 1).

Vitiello et al does not teach that the chemotherapy is temozolomide.

Friedman et al teach successful treatment of glioblastoma multiforme in patients comprising administering temozolomide (abstract; Table 4; p. 2592, col. 1; Fig. 2). Friedman et al teach that combining two or more drugs that have different cytotoxic mechanisms or are subject to different mechanisms of resistance can produce

synergistic effects. Temozolomide can be coadministered with various agents (p. 2593, col. 1; p. 2594, col. 1, last para).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use temozolomide as the chemotherapeutic in the method taught by Vitiello et al because Friedman et al teach using temozolomide to treat glioblastoma multiforme. One would have been motivated to use temozolomide as the chemotherapeutic in the method taught by Vitiello et al because Friedman et al demonstrate that temozolomide successfully and safely treats glioblastoma multiforme and expressly suggests combining temozolomide with other agents that use different cytotoxic mechanisms to produce synergistic effects. One of ordinary skill in the art would have a reasonable expectation of success treating glioblastoma multiforme with DC and temozolomide because both agents are known to treat glioblastoma multiforme.

Further, each of the agents, DC and temozolomide, had been taught by the prior art to be used for treating cancer, particularly glioblastoma multiforme, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant method claims, given the teaching of the prior art using DC or temozolomide to treat glioblastoma multiforme, it would have been obvious to combine the two agents for the treatment of glioblastoma multiforme

because the idea of doing so would have logically followed from their having been individually taught in the prior art to be useful as agents for the same purpose of treating glioblastoma multiforme. One of ordinary skill in the art could have combined the two agents and each agent would have performed the same function of treating glioblastoma multiforme as they would have separately. One of ordinary skill in the art would have recognized the results of such a combination of agents as predictable.

3. Claims 5-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Application Publication 2002/0119121, Vitiello et al, filed 9/6/2001, published 8/29/2002, and Friedman et al (Clinical Cancer Research, 2000, 6:2585-2597) as applied to claims 1-3, 10 and 11 above, and further in view of Liu et al (J of Immunotherapy, July/August 2003, 26:301-312).

The claims are drawn to the method of claim 1, wherein administering said at least one vaccination further comprises administering at least three vaccinations of DC (claim 5), wherein each of said at least one vaccination comprises from about 10^5 to about 10^7 DC (claim 6), wherein each of said at least one vaccination of DC comprises about $10X10^6$ to about $40X10^6$ DC (claim 7).

Vitiello et al and Friedman et al teach a method of treating a disease, or glioblastoma multiforme in a mammal comprising administering at least one vaccination of DC to said mammal and administering a regimen of temozolomide chemotherapy after DC administration as set forth above.

Vitiello et al and Friedman et al (the combined references) do not teach administering at least three vaccinations of DC, wherein each of said at least one vaccination comprises from about 10^5 to about 10^7 DC, or about $10X10^6$ to about $40X10^6$ DC.

Liu et al teach a method of treating glioblastoma multiforme in a patient comprising administering autologous DC primed *ex vivo* with tumor antigen at a dose of $10X10^6$ to $40X10^6$ three times (p. 308, col. 2). Several of the patients produced a cytotoxic T-cell response to their own tumor cells *in vitro* (p. 310, col. 2; p. 311, col. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the DC in the method taught by the combined references at dosages of $10X10^6$ to $40X10^6$ at least three times because Liu et al teach this dose and administration regimen can be safely used in subjects for treatment of glioblastoma multiforme. One would have been motivated to use this dose and administration regimen in order to treat glioblastoma multiforme by eliciting a cytotoxic T-cell response to the tumor. One of ordinary skill in the art would have a reasonable expectation of success using this dose and administration regimen because Liu et al demonstrate it can be successfully and safely administered to glioblastoma multiforme patients to elicit a cytotoxic T cell response for treatment.

Relevant Arguments

4. Applicants argue that Vitiello does not describe a method for treating a disease condition in a mammal by administering at least one vaccination of DC prior to

administering a regimen of chemotherapy. Applicants argue that Vitiello is primarily concerned with methods of inducing $CD8^+$T lymphocytes *ex vivo* and treating patients by administering the T lymphocytes. Applicants appear to argue that Vitiello teaches away from using chemotherapy and cite paragraph [0004]. Applicants also cite paragraph [0135] and argue that neither paragraph suggests methods in which a mammal is administered chemotherapy after DC. Applicants argue that Vitiello discusses administration of CTLs with conventional therapy and discusses DC vaccination in the following paragraph, as another application of the invention. Applicants argue that no suggestion to practice DC vaccination in conjunction with conventional therapy or a chemotherapeutic treatment regimen (p. 10-11).

The arguments have been considered but are not found persuasive. Applicants have argued and discussed the Vitiello reference individually without clearly addressing the combined teachings. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

With regards to Applicants' arguments that the main focus of Vitiello is not DC administration, the arguments are not persuasive because Vitiello clearly teaches

administering DC for cancer/disease treatment, whether alone or in a mixture with other immune cells.

With regards to Applicants' arguments for Vitiello teaching away form the use of chemotherapy, the arguments are not persuasive because Vitiello clearly teaches using chemotherapy in combination with administering DC or DC mixtures as well as administering the DC or mixtures prior to chemotherapy, as set forth above. MPEP 2131.05 states: A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. The question whether a reference "teaches away" from the invention is inapplicable to an anticipation analysis. Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The prior art was held to anticipate the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed."). See also Atlas Powder Co. v. IRECO, Inc., 190 F.3d 1342, 1349, 51 USPQ2d 1943, 1948 (Fed. Cir. 1999) (Claimed composition was anticipated by prior art reference that inherently met claim limitation of "sufficient aeration" even though reference taught away from air entrapment or purposeful aeration.). Additionally, also applicable to Applicants' arguments above that Vitiello focuses on inducing $CD8^+$T lymphocytes *ex vivo* and treating patients by administering the T lymphocytes, MPEP 2123 states: Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). Vitiello teaches administering DC, DC mixtures, and administering

these compositions of their invention before chemotherapy, hence Vitiello anticipates administering chemotherapy and administering DC cells.

5. Applicants argue that Friedman does not contain any suggestion to use temozolomide in conjunction with a cell-based therapeutic treatment much less DC administration (p. 11).

The arguments have been considered but are not found persuasive. Applicants have argued and discussed the Friedman reference individually without clearly addressing the combined teachings. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. It is the combination of all of the cited and relied upon references which made up the state of the art with regard to the claimed invention. Applicant's claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As stated above, each of the agents, DC and temozolomide, had been taught by the prior art to be used for treating cancer, particularly glioblastoma multiforme, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same

purpose since the idea of combining them flows logically from their having been individually taught in the prior art.

6. Applicants argue that in the instant application, a trial was conducted in which glioblastoma multiforme patients were treated with DC vaccination, chemotherapy, or DC followed by chemotherapy. Applicants argue that patients treated with chemotherapy after DC vaccination had significantly delayed tumor progression and significantly prolonged survival relative to patients receiving either treatment individually. Applicants argue that the claimed methods provide significant benefits not taught or suggested by the cited references (p. 11-12).

The arguments have been considered but are not found persuasive. As stated in the above rejection, each of the agents, DC and temozolomide, had been taught by the prior art to be used for treating cancer, particularly glioblastoma multiforme, thus the instant situation is amenable to the type of analysis set forth in In re Kerkhoven, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two modes of treatment, each of which is taught by the prior art to be useful for the same purpose in order to make a protocol that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Further, one would one of ordinary skill in the art could have combined the two agents and each agent would have performed the same function of treating glioblastoma multiforme as they would have separately. One of ordinary skill in the art would have recognized the results of such a combination of

agents as predictable and would have expected additive effects that are greater than either alone, given both agents contribute to treatment. MPEP 716.02(c) states: "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." In re Gershon, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967). Further, MPEP 716.02(b) states: The evidence relied upon should establish "that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance." Ex parte Gelles, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). Although the specification discloses significantly improved outcome for patients receiving DC vaccination followed by chemotherapy compared to patients treated with either alone, it appears the combination of chemotherapy and DC vaccination results in the improvement and no comparison is made to suggest that the sequence of administration of DC before chemotherapy gives unexpected results because no comparison is made to the sequence of administering chemotherapy before DC vaccination. Therefore, one of ordinary skill in the art would reasonably expect improved results by combining temozolomide treatment with DC vaccination as compared to either alone because it is the combination of two known treatments that would have an expected greater result than either alone. Applicants have not met their burden to established that the results of the instant claims would be unexpected or unobvious compared to the combination treatment taught by the combined prior art.

Finally, it is noted that whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective

evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980) (MPEP 716.02(d)). The arguments provided by Applicants are drawn only to the Examples in the specification with regards to treatment of glioblastoma multiforme using *ex vivo* primed autologous DC in combination with various chemotherapeutics, of which are limitations not recited in all the claims nor commensurate in scope with the broadly claimed methods.

7. All other rejections recited in the Office Action mailed October 18, 2007 are hereby withdrawn.

8. **Conclusion:** No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. ' 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. ' 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY

PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Laura B Goddard, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643